

REMARKS

Claims 7-12, 14-16 and 18 are pending. Claims 7, 8 and 18 have been amended. Claims 1-6, 13 and 17 were previously cancelled without prejudice. Support for amended claims 7, 8, 12, 16 and 18 can be found throughout the specification. It is respectfully submitted that no new matter has been introduced in this amendment.

I. Sequence Compliance

The Examiner has issued a Notice to Comply, which is enclosed herewith, as required in the Office Action. Applicant has addressed the deficiencies set forth in the Notice to Comply, as set forth above.

I. Claim Objections

In the Office Action, The Examiner stated that each of the claims is not presented as an object of a sentence starting with "We claim" or "The invention claimed is," as per MPEP 608.01(m). In response, the specification has been amended to add the phrase "We claim".

In the Office Action, the Examiner also requested substitution of the phrase "A therapeutic agent for hepatitis C" in claims 12 and 16 with "A therapeutic agent for treating hepatitis C infection". In order to expedite prosecution, this change has been made, without prejudice.

III. Rejection under 35 U.S.C. § 102

Elbashir Reference

In the Office Action, the Examiner rejected claims 7, 8 and 18 as being anticipated by Elbashir et al. 2002 (Methods, v.26:199-213). The Examiner specifically asserted that the phrase "a nucleotide sequence" (recited in claims 7, 8 and 18) refers to any sequence of nucleotide from as few as 2 to as many as 20 nucleotides included in SEQ ID No. 23. The Examiner continued by noting that "this is distinct from the phrase "the nucleotide sequence", which according to the Examiner requires the entirety of SEQ ID No. 23.

According to the Examiner, the Elbashir reference teaches the siRNA duplex, GL2 (Figure 4B on page 205) which comprises the sequence “CU”, which is also found in SEQ ID No. 23.

Applicant has amended the phrase “a nucleotide sequence shown in SEQ ID No. 23” in claims 7, 8 and 18 to read “the nucleotide sequence shown in SEQ ID No. 23”. Therefore, Applicants respectfully request that the Examiner’s rejection be removed.

Elbashir Reference

In the Office Action, the Examiner rejected claims 7, 8, 11 and 18 as being anticipated by Yu, et al. (2002, PNAS, v.99:6047-52). The Examiner specifically asserted that the phrase “a nucleotide sequence” (recited in claims 7, 8 and 18) refers to any sequence of nucleotide from as few as 2 to as many as 20 nucleotides included in SEQ ID No. 23. The Examiner continued by noting that “this is distinct from the phrase “the nucleotide sequence”, which according to the Examiner requires the entirety of SEQ ID No. 23.

According to the Examiner, the Yu reference teaches expression plasmids (vectors) comprising siRNAs shown in Figure 4A and that these siRNA’s comprise the sequence, “CU”, which is also found in SEQ ID No. 23.

Applicant has amended the phrase “a nucleotide sequence shown in SEQ ID No. 23” in claims 7, 8 and 18 to read “the nucleotide sequence shown in SEQ ID No. 23”. Claim 11 depends from claim 7. Therefore, Applicants respectfully request that the Examiner’s rejection be removed.

Elbashir Reference

In the Office Action, the Examiner rejected claims 7, 8, 11, 12, 16 and 18 as being anticipated by Jadhav, et al. (U.S. Patent Application Publication 2005/0209180). The Examiner specifically asserted that the phrase “a nucleotide sequence” (recited in claims 7, 8 and 18) refers

to any sequence of nucleotide from as few as 2 to as many as 20 nucleotides included in SEQ ID No. 23. The Examiner continued by noting that “this is distinct from the phrase “the nucleotide sequence”, which according to the Examiner requires the entirety of SEQ ID No. 23. The Examiner further noted that claims 12 and 16 are directed to a therapeutic agent for hepatitis C wherein the active ingredient is the siRNA of claim 7 and that therefore an siRNA meeting the structural limitations of claim 7 would be presumed to perform as a therapeutic agent for hepatitis C.

According to the Examiner, the Jadha reference teaches siRNAs targeting HCV for the treatment of HCV-related diseases and conditions and that the Jadha reference teaches an siRNA comprising a sense strand having SEQ ID NO: 298 and an antisense strand having SEQ ID No.: 994. The Examiner alleges that this siRNA comprises 19 nucleotides of SEQ ID No. 23.

Applicant has amended the phrase “a nucleotide sequence shown in SEQ ID No. 23” in claims 7, 8 and 18 to read “the nucleotide sequence shown in SEQ ID No. 23”. Claims 11 and 12 depend directly from claim 7. Claim 16 depends from claim 11. Therefore, Applicants respectfully request that the Examiner’s rejection be removed.

Applicant also wishes to correct the Examiner’s characterization of the Jadhav reference. At page 6, lines 3-4 of the Office Action, the Examiner states that “This siRNA comprises 19 nucleotides of the instantly claimed SEQ ID NO:23”. However, Applicants respectfully point out that the phrase “19 nucleotides” is not accurate and that the siRNA of the Jadha reference actually has 17 nucleotides. Specifically, the siRNA disclosed in Jadhav comprising SEQ ID NO:298 and DEQ ID NO:994 does not have the three nucleotides at the 3’ end of DEQ ID NO. 23 of the present invention.

IV. Rejection under 35 U.S.C. § 103

In the Office Action, the Examiner rejected claims 7, 8, 11, 16 and 18 under 35 U.S.C. § 103(a) as being obvious over Seki, et al., Bass and Yu.

In the Office Action, the Examiner rejected the present invention alleging that the Seki reference teaches an antisense nucleotide targeting HCV and complementary to SEQ ID NO: 23 and that it is 20 nucleotides in length.” See Office Action, page 7. The Office Action further states “Bass provides a motivation to make a double-stranded RNA instead of an antisense oligonucleotide by teaching that RNA interference is more robust than antisense techniques by decreasing expression to lower levels and working at much lower concentrations than antisense.” The Office Action then concludes that “one of ordinary skill in the art would recognize that targeting HCV with an siRNA corresponding to SEQ ID No: 23 would be a more effective antiviral agent than just the antisense taught by Seki, et al.” Office Action at page 8. The Examiner also argues that “Yu provides a reason to express siRNAs from vectors be (sic) teaching that such expression is more economical than chemical siRNA synthesis and may be more practical than using chemically-synthesized siRNAs for *in vivo* applications.” Office Action at page 8.

The Seki reference discloses SEQ ID No. 83 (SMS 19), which is partially complimentary to SEQ ID No. 23 of the present application. The Examiner’s attention is directed to the fact that the Seki reference does not provide any experimental result or data supporting the effectiveness of the nucleotide of SEQ ID No. 83 (SMS 19). Applicants respectfully submit that one of ordinary skill in the art viewing the Seki reference would not understand whether the nucleotide has an antiviral activity.

Seki, at page 57, line 21 to page 58, line, states:

It was also found that antisense compounds corresponding to a region other than a particular region in HCV polypeptide are definitely ineffective. It has been determined that said particular region corresponds to the base sequence from positions 107 to 199, preferably from 127 to 180, of the SEQ ID No. 1 of Sequence Listing. Thus it is believed that all of the target sequences of antisense compounds are fallen within the above scope.

The target sequence of the nucleotide of SEQ ID No. 83 (SMS 19) is the sequence from positions 351 to 370 of the SEQ ID No. 1. This target is clearly outside of the “particular

region”, and therefore, under the teaching of the Seki reference, the nucleotide of SEQ ID No. 83 (SMS 19) is “definitely ineffective”. As a result, one of skill in the art would not reasonably expect that SEQ ID No. 83 (SMS 19) is effective as an antisense compound based on the teachings of the Seki reference.

Further, Seki provides another disincentive for those of skill in the art to employ the nucleotide of SEQ ID No. 83 (SMS 19). The Seki reference, at page 34, lines 2-25, reads:

Although the amount of the produced HCV core protein was decreased by SMS 3, this antisense compound has affected also the translation of E. Coli β -lactamase mRNA to some extent.

Thus, the Seki reference teaches that deciding a target sequence may cause a decrease in specificity, and therefore the decision needs to be made cautiously.

The Seki document cited by the Examiner, which is a Canadian patent document, has a Japanese counterpart, JP patent publication No. H06-311885 (1994) (JP patent application No. H05-217095 (1993)). The Japanese counterpart, at paragraph [0053], reads: “Although the amount of the produced HCV core protein was decreased by Anti 3, this antisense compound has affected also the translation of E. Coli β -lactamase mRNA to some extent.” (It should be noted that although this sentence corresponds to the above quoted sentence in the cited Canadian Seki reference, it refers to Anti-3, rather than SMS3). An English translation of JP patent publication No. H06-311885 (1994) was filed with the European patent Office. Applicant refers the Examiner to the first four lines on page 38 of the English translation.

In the Seki reference, the target sequence for the nucleotide of “Anti 3” is the sequence from positions 362 to 376 of SEQ ID No. 1, which partially overlaps with the sequence of positions 351 to 370 of SEQ ID No. 1 targeted by SEQ ID No: 83 (SMS 19). One of skill in the art would be concerned that SEQ ID No. 83 (SMS 19) would also have insufficient specificity in the same manner as Anti 3.

As a result, one of skill in the art would not be motivated to employ SEQ ID No. 83 (SMS 19) disclosed in the Seki reference, even as an antisense DNA, because (i) the Seki reference does not mention the activity of the sequence, (ii) the sequence corresponds to a region other than the particular region of positions 107 to 199 of HCV polypeptide, and is therefore suggested to be “definitely ineffective” by the document, and (iii) the Japanese counterpart of the document suggests that the sequence may have insufficient specificity as an antisense DNA.

In view of the above, it would be even more difficult for one of skill in the art to arrive at the siRNA having the sequence of SEQ ID No. 23 of the present invention based on SEQ ID No. 83 (SMS 19) as disclosed in the Seki reference. One of skill in the art viewing the Seki reference would therefore be discouraged from using SEQ ID No. 83 as a starting point for developing siRNA's.

With regard to the Bass reference, Applicants' again explain that the Bass reference does not mention that a siRNA having a nucleotide sequence complementary to an antisense DNA is more effective than the antisense DNA. In fact, the Bass reference is silent about the relationship between a nucleotide sequence of a siRNA and that of an antisense DNA. The Bass reference, as cited by the Examiner in the Office Action, merely describes that RNA interference techniques are better than antisense techniques, in general terms. Applicants respectfully submit that due to the difference of mechanisms between siRNAs and antisense DNAs, a person of ordinary skill in the art would not expect that a siRNA having a nucleotide sequence complementary to a known antisense DNA is more effective than the antisense DNA.

Thus, a person of ordinary skill in the art who reads the cited documents would not expect that the siRNA having a nucleotide sequence of the instant SEQ ID No: 23 of the present invention is more effective in suppressing a target gene expression than the antisense DNA having a nucleotide sequence of SEQ ID No. 83 taught by Seki et al.

Finally, the Office Action cites the Yu, et al. reference stating that “Yu, et al. teach that siRNAs can be expressed from a vector. However, Yu does not teach or suggest “an siRNA having a nucleotide sequence shown in SEQ ID No. 23” as recited in amended independent claims 9 and 18 of the present invention. Therefore, the Yu et al. reference does not cure the deficiency of the Seki, et al. and Bass references.

In view of the above, Applicants respectfully request withdrawal of the rejection of claims 7, 8, 11, 16 and 18 under 35 U.S.C. § 103(a) as being obvious over Seki, et al. (1994, CA2104649), Bass (2001, Nature v. 411: 428-429, and Yu, et al. (2002, PNAS, v.99:6047-52).

V. Double Patenting

The Examiner provisionally rejected claims 11 and 16 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 16-18, 25 and 26 of copending Application No. 10/567,168 in view of Jadhav. In doing so, the Examiner acknowledged that the Jadhav application does not teach a vector comprising an siRNA having a sequence of the instant SEQ ID No.:23.

According to the Examiner, the Jadha reference teaches siRNAs targeting HCV for the treatment of HCV-related diseases and conditions and that the Jadha reference teaches an siRNA comprising a sense strand having SEQ ID NO: 298 and an antisense strand having SEQ ID No.: 994. The Examiner alleges that this siRNA comprises 19 nucleotides of SEQ ID No. 23.

Applicant wishes to correct the Examiner’s characterization of the Jadhav reference. At page 6, lines 3-4 of the Office Action, the Examiner states that “This siRNA comprises 19 nucleotides of the instantly claimed SEQ ID NO:23”. However, Applicants respectfully point out that the phrase “19 nucleotides” is not accurate and that the siRNA of the Jadha reference actually has 17 nucleotides. Specifically, the siRNA disclosed in Jadhav comprising SEQ ID

NO:298 and DEQ ID NO:994 does not have the three nucleotides at the 3' end of DEQ ID NO. 23 of the present invention.

Applicant has amended the phrase "a nucleotide sequence shown in SEQ ID No. 23" in claim 7 to read "the nucleotide sequence shown in SEQ ID No. 23". Claim 11 depends directly from claim 7. In view of this amendment, applicants respectfully submit that claim 7, and claim 11 dependent thereon, are not obvious in view of claims 16-18, 25 and 26 of the Jadhav application. Therefore, Applicants respectfully request that the Examiner's rejection be removed.

Conclusion

This Amendment is being submitted together with a petition for a 3-month extension of time and a PTO Form 1449 and accompanying IDS. If it is determined that additional fees are due or that any fee has been overpaid, the Commissioner for Patents is hereby authorized to charge said fee or credit any overpayment to Deposit Account No. 50-0552.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
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Notice to Comply

Application No.

10543078

Examiner

JENNIFER PITRAK

Applicant(s)

KOHARA ET AL.

Art Unit

1635

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: The specification fails to use the sequence identifiers ("SEQ ID NO:___") when referring to sequences that are part of the Sequence Listing as is required per 37 C.F.R. 1.821(d). For example, see Figures 1, 2, 4, and 6-9 (or Figure descriptions on pages 4-5), line 30 on page 14, lines 10-11 on page 16, Table 1 on page 17, last paragraph on page 18, and line 5 on page 19.

Applicant Must Provide:

- ☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the specification.**
- ☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510

For CRF Submission Help, call (571) 272-2501/2583.

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